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(54) Title: GABA AND L-GLUTAMIC ACID ANALOGS FOR ANTISEIZURE TREATMENT

(57) Abstract

Novel analogs of GABA and L-glutamic acid are used for treating seizure disorders. One analog, 4-amino-3-(2-methylpropyl) butanoic acid is found to have unexpectedly potent antiseizure activity *in vivo*.

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**GABA AND L-GLUTAMIC ACID ANALOGS
FOR ANTISEIZURE TREATMENT**

TECHNICAL FIELD

5

The present invention relates to novel compounds that are analogs of glutamic acid and gamma-aminobutyric acid (GABA). More specifically, the analogs are useful as antiseizure therapy for 10 central nervous system disorders such as epilepsy, Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive dyskinesia and spasticity. It is also possible that the present invention could be used as an anti-depressant, anxiolytic and 15 antipsychotic activity.

BACKGROUND OF THE INVENTION

Gamma-aminobutyric acid (GABA) and L- 20 glutamic acid are two major neurotransmitters involved in the regulation of brain neuronal activity. GABA is the major inhibitory neurotransmitter and L-glutamic acid is an excitatory transmitter (1,2). An imbalance in the concentration 25 of these neurotransmitters can lead to convulsive

states. Accordingly, it is clinically relevant to be able to control convulsive states by controlling the metabolism of this neurotransmitter.

When the concentration of GABA diminishes 5 below a threshold level in the brain, convulsions result (3); when the GABA levels rise in the brain during convulsions, seizures terminate (4). The term seizure as used herein means excessive unsynchronized neuronal activity that disrupts normal neuronal 10 function. In several seizure disorders there is concomitant with reduced brain GABA levels a diminished level of L-glutamic acid decarboxylase (GAD) activity also observed (5-9). Often, the concentrations of GAD and GABA vary in parallel 15 because decreased GAD concentration results in lower GABA production.

Because of the importance of GABA as an inhibitory neurotransmitter, and its effect on convulsive states and other motor dysfunctions, a 20 variety of approaches have been taken to increase the brain GABA concentration. For example, the most obvious approach was to administer GABA. When GABA is injected into the brain of a convulsing animal, the convulsions cease (10). However, if GABA is 25 administered systemically, there is no anticonvulsant effect because GABA, under normal circumstances,

cannot cross the blood brain barrier (11). In view of this limitation, there are three alternative approaches that can be taken to raise GABA levels.

The most frequent approach is to design a
5 compound that crosses the blood brain barrier and then inactivates GABA aminotransferase. The effect is to block the degradation of GABA and thereby increase its concentration. Numerous mechanism-based inactivators of GABA aminotransferase are known (12).

10 Another approach is to increase GABA concentrations in the brain by making GABA lipophilic by conversion to hydrophobic GABA amides (13,14), imines (13), or GABA esters (15,16) so that GABA can cross the blood brain barrier. Once inside the
15 brain, these compounds require amidases and esterases to hydrolyze off the carrier group and release GABA.

A third approach is to increase brain GABA levels by designing an activator of GAD. A few compounds have been described as activators of GAD.
20 The anticonvulsant agent, milacemide, was reported to increase the activity of GAD by 11% and as a result increase GABA concentration in the substantia nigra by up to 38% (17). The anticonvulsant drug sodium valproate (18) was also reported to activate GAD and
25 increase GABA levels.

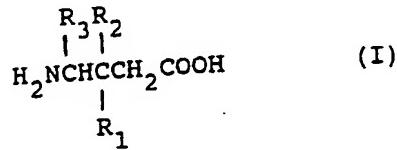
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Applicant has synthesized a series of GABA and L-glutamate analogs having the ability to activate GAD in vitro and having a dose dependent protective effect of seizure in vivo. One compound in particular was found to be an unexpectedly potent suppressor of seizures while the entire series of drugs do not promote the unwanted side effects of ataxia. Accordingly, the present invention provides a novel series of compounds and their method of use in suppressing seizures.

SUMMARY OF THE INVENTION

In accordance with the present invention,
15 there is provided a compound of the formula I



20 wherein R_1 is a straight or branched alkyl of from 1 to 6 carbons, phenyl or cycloalkyl having from 3 to 6 carbon atoms, R_2 is hydrogen or methyl, and R_3 is hydrogen, methyl or carboxyl; or its diastereomers, 25 or enantiomers and pharmaceutically acceptable salts thereof.

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The present invention further provides a method of treating seizure disorders by administering an anticonvulsant effective amount of the aforesaid composition.

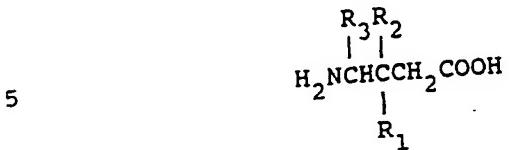
5 Also, the present invention provides a method for increasing brain neuronal GABA and provides pharmaceutical compositions of the compounds of Formula I.

10

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a series of 3-alkyl-4-aminobutyric acid or 3-alkyl glutamic acid analogs which are shown 15 herein to activate GAD. For example, the alkyl moieties as represented by R_1 in Formula I can be methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, isopentyl and neopentyl as well as other alkyl groups. The cycloalkyl groups 20 represented by R_1 are exemplified by cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The analogs are further shown herein to prevent seizure while not causing the side effect of ataxia, such a side effect being found in several anti-seizure pharmaceuticals.

More specifically, the present invention provides compounds of the formula I



wherein R₁ is a straight or branched alkyl of from 1 to 6 carbons, phenyl or a cycloalkyl having 3 to 6 10 carbon atoms R₂ is hydrogen or methyl, and R₃ is hydrogen, methyl, or carboxyl; or its diastereomers; or enantiomers, and both pharmaceutically acceptable salts thereof. The most preferred compounds of the present invention are of the formula above wherein R₃ 15 is hydrogen, R₂ is hydrogen and R₁ isobutyl. That is, the preferred compound is 4-amino-3-(2-methylpropyl) butanoic acid. It has been found that this compound is unexpectedly more potent than the other analogs synthesized in accordance herewith and 20 tested in vivo. What is further surprising, as the following data shows, is that this preferred compound is the least effective one of the analogs tested in activating GAD in vitro. Accordingly, it was very unexpected that this preferred compound had such a 25 high potency when tested in vivo.

The compounds made in accordance with the present invention may form pharmaceutically acceptable salts with both organic and inorganic acids or bases. For example, the acid addition salts 5 of the basic compounds are prepared either by dissolving the free base in aqueous or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution. Examples of 10 pharmaceutically acceptable salts are hydrochlorides, hydrobromides, hydrosulfates, etc. as well as sodium, potassium and magnesium etc. salts.

The compounds made in accordance with the present invention can contain one or several 15 asymmetric carbon atoms. The invention includes the individual diastereomers or enantiomers, and the mixtures thereof. The individual diastereomers or enantiomers may be prepared or isolated by methods already well known in the art.

20 The method for the formation of the 3-alkyl-4-aminobutanoic acids starting from 2-alkenoic esters is prepared from commercially available aldehydes and monoethyl malonate by the Knoevenagel reaction (19), with the exception of ethyl 4,4-25 dimethyl-2-pentenoate. This compound was prepared from 2,2-dimethylpropanal and ethyl lithioacetate,

followed by dehydration of the beta-hydroxyester with phosphoryl chloride and pyridine. The Michael addition of nitromethane to alpha, beta-unsaturated compounds mediated by 1,1,3,3-tetramethylguanidine or 5 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) afforded 4-nitroesters in good yields.

Although the aliphatic nitro compounds are usually reduced by either high pressure catalytic hydrogenation by metal-catalyzed transfer 10 hydrogenation, or by newly introduced hydrogenolysis methods with ammonium formate or sodium borohydride and palladium as catalysts, applicants have found that 4-nitrocarboxylic esters can be reduced almost quantitatively to the corresponding 4-aminocarboxylic 15 esters by hydrogenation using 10% palladium on carbon as catalysts in acetic acid at room temperature and atmospheric pressure. The amino esters produced were subjected to acid hydrolysis to afford the subject inventive compounds in good yields. This procedure 20 provides access to a variety of 3-alkyl-4-aminobutanoic acids as listed in Tables 1 and 2 as examples and thus is advantageous in comparison to methods previously used.

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When the starting material is not commercially available, the synthetic sequence was initiated with the corresponding alcohol, which was oxidized to the aldehyde by the method of Corey et al 5 (20).

The compounds made by the aforementioned synthetic method can be used as pharmaceutical compositions as an anti-depressant, anxiolytic, antipsychotic, antiseizure, anti-dyskinetic, or 10 anti-symptomatic for Huntington's or Parkinson's diseases when an effective amount of a compound of the aforementioned formula together with a pharmaceutically acceptable carrier is used. That is, the present invention provides a pharmaceutical 15 composition for the suppression of seizures resulting from epilepsy, the treatment of cerebral ischemia, Parkinson's disease, Huntington's disease and spasticity and also possibly for antidepressant, anxiolytic and antipsychotic effects. These latter 20 uses are expected due to functional similarities to other known compounds having these pharmacological activities. The pharmaceutical can be used in a method for treating such disorders in mammals, including human, suffering therefrom by administering 25 to such mammals an effective amount of the compound as described above in unit dosage form.

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The pharmaceutical compound made in accordance with the present invention can be prepared and administered in a wide variety of dosage forms.

- For example, these pharmaceutical compositions can be 5 made in inert, pharmaceutically acceptable carriers which are either solid or liquid. Solid form preparation include powders, tablets, dispersible granules, capsules, cachets, and suppositories. Other solid and liquid form preparations could be 10 made in accordance with known methods of the art.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from one milligram to about 300 milligrams per kilogram daily, based on an average 70 kilogram patient. A 15 daily dose range of about 1 milligram to about 50 milligrams per kilogram is preferred. The dosages, however, may be varied depending upon the requirement with a patient, the severity of the condition being treated, and the compound being employed.

- 20 Determination of the proper dosage for particular situations is within the skill of the art.

Illustrative examples of compounds made in accordance with the present invention were tested to demonstrate the ability of the compounds to activate 25 GAD in vitro and to prevent seizure in vivo without the side effect of ataxia.

In Vitro GAD Activation

Assays were carried out in 10 ml vials sealed with serum caps through which a center well (Kontes catalogue no. 882320-000) was inserted. The 5 center well was charged with 200 μ l of freshly prepared 8% KOH solution. Various concentrations of L-glutamic acid (0.5, 0.25, 0.166, 0.125, 0.10 mM) containing [14 C]L-glutamate (10 μ Ci/mmol) in 50 mM potassium phosphate buffer, pH 7.2 were shaken at 10 37°C in separate vials with purified L-glutamic acid decarboxylase (18.75 μ g; spec. act 10.85 μ mol/min mg) in a total volume of 2.00 ml. After being shaken for 60 minutes, the enzyme reactions were quenched by the addition of 200 μ l of 6 M sulfuric acid to the 15 contents of each of the vials. The vials were shaken for an additional 60 minutes at 37°C. The center wells were removed and placed in scintillation vials with 10 ml of scintillation fluid for radioactivity determination. The same assays were repeated except 20 in the presence of various concentrations of the activators (2.5, 1.0, 0.5, 0.25, 0.1, 0.05 mM). The V_{max} values were determined from plots of 1/cpm versus 1/[glutamate] at various concentrations of activators. The data were expressed as the ratio of 25 the V_{max} in the presence of the activators to the V_{max} in the absence of the activators times 100%.

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The results of the experiment are shown in Table 1. The tests show that there was significant activation by the various compounds tested to differing degrees. The known activator sodium valproate and GABAPENTIN were tested.

In vivo tests were performed to demonstrate the seizure preventing capabilities of the novel compounds. Threshold maximum electroshock is an animal model test for generalized seizures that is similar to that of Piredda, S.G. et al (21). The methods for this test are described as follows.

Male CF-1 mice (22-30 grams) were allowed free access to food and water prior to testing. For screening, groups of five mice were given a compound intravenously at doses of 30, 100, and 300 mg/kg and tested at 0.5, 2.0 and 4.0 hours after dosing. Drugs were either dissolved in 0.9% saline or suspended in 0.2% methylcellulose. Animals were shocked with corneal electrodes (see below) and observed for tonic hindlimb extensor seizures. Absence of hindlimb extension was taken as an anticonvulsant effect.

The electroshock apparatus delivered a 60 Hz sine wave with a current amplitude of 14 mA (peak-to-peak) for 0.2 seconds. The current strength of 14 mA used in this procedure produced tonic

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extensor seizures in approximately 95% of untreated mice, but was only slightly above threshold for tonic extension.

Summaries of the numbers of animals.

5 protected from seizures when tested 120 minutes after administration of each compound set forth in the lefthand column are given in Table 2 for varying dose levels set forth in the second column of the Table.

Due to the interesting phenomena related to
10 the (R,S)-i-butyl GABA (the compound having significantly higher potency and effectiveness without causing ataxia), threshold maximal electroshock tests where conducted varying the time of testing from one hour to eight hours, the dose
15 being 10 milligram per kilogram in mice, injected intravenously. Table 3 shows the results of these tests indicating a maximum protection after two hours of testing.

In view of the above results, a dose
20 response curve was made for the two hour testing time period in mice, the drug being given intravenously at 10 milligrams per kilogram. The results of this test is shown in Table 4 with a calculated ED50 equaling 2.07 milligrams per kilogram.

A third pharmacological test was performed as described in R.L. Krall et al (22). In this procedure, drugs were tested for attenuation of threshold clonic seizures in mice caused by 5 subcutaneous administration of pentylenetetrazol (85 mg/kg) which is a generally accepted model for absence type seizures. Results from the third test for the compound when administered either intravenously or orally is shown in Table 5. The 10 test was conducted at three dose levels, showing effective protection at 30 mg/kg and 100 mg/kg with no ataxia.

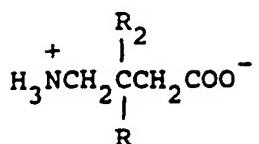
The above is a significant finding because the compound having the least ability to activate GAD 15 surprisingly had an approximately 10 fold increase in potency over the other compounds tested. Even more unexpected is the absence of ataxic side effect coupled to this increase in potency.

In view of the above demonstrated activity 20 of the compounds characterizing the present invention and in particular the 4-amino-3-(2-methylpropyl)butanoic acid (isobutyl GABA) the compounds made in accordance with the present invention are of value as pharmacological agents, 25 particularly for the treatment of seizures in mammals, including humans.

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TABLE 1

Activation of GAD by GABA analogues at various concentrations expressed in %

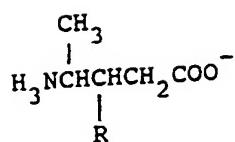


R_1, R_2	2.5mM	1.0mM	0.5mM	0.25mM	0.1mM	0.05mM
(R,S)-CH ₃ ,H	239	168	142	128	118	107
(R)-CH ₃ ,H	327	202	185	135	128	109
(S)-CH ₃ ,H	170	118	--	103	--	-
CH ₃ , CH ₃	174	125	--	109	--	-
(R,S)-C ₂ H ₅ ,H	172	128	--	108	--	-
(R,S)-n-C ₃ H ₇ ,H	156	112	--	105	--	-
(R,S)-i-C ₃ H ₇ ,H	140	108	--	104	--	-
(R,S)-n-C ₄ H ₉ ,H	178	117	--	105	--	-
(R,S)-i-C ₄ H ₉ ,H	143	113	--	109	--	-
(R,S)-s-C ₄ H ₉ ,H	169	119	--	105	--	-
(R,S)-t-C ₄ H ₉ ,H	295	174	147	121	117	108
(R,S)-neo-C ₅ H ₁₁ ,H	279	181	--	130	--	-
(R,S)-i-C ₅ H ₁₁ ,H	142	118	--	109	--	-
(R,S)-C ₆ H ₁₁ ,H	125	100		100		
(R,S)-C ₆ H ₅ ,H	218	129	--	110	--	-

^a Not determined

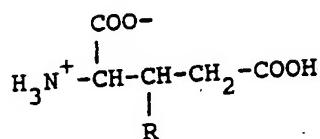
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R	2.5mM	1.0mM	0.5mM	0.25mM	0.1mM	0.05mM
H(R,S)	140	111	--	104	--	--
H(R)	173	125	--	108	--	--
H(S)	100	100	--	100	--	--
CH ₃	143	121	--	109	--	--
C ₆ H ₅	207	151	--	112	--	--
Sodium Valproate	207	138	124	119	115	105
GABAPENTIN	178	145	--	105	--	--

Activation of GAD by glutamate analogues expressed in %.



R	2.5mM	1.0mM	0.25mM
CH ₃	212	144	113
C ₂ H ₅	170	128	113
n-C ₃ H ₇	153	125	108
i-C ₃ H ₇	144	114	105
n-C ₄ H ₉	133	117	105
i-C ₄ H ₉	129	112	106
C ₆ H ₅	172	135	112
Sodium Valproate	207	138	119

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TABLE 2

Prevention of tonic extensor seizures in mice
following intravenous administration of 3-substituted
GABA derivatives.

R	dose (mg/kg)	time after dose (min)	effect #protected/ # tested	ataxia # ataxia/ # tested
(R,S)-CH ₃	10	120	0/5	0/5
	30	120	4/5	0/5
	100	120	3/5	0/5
(R)-CH ₃	1	120	1/10	0/10
	3	120	2/10	0/10
	10	120	4/10	0/10
	30	120	3/10	0/10
	100	120	3/10 (5/10)	1/10
(S)-CH ₃	10	120	1/10	1/10
	30	120	2/10	0/10
	100	120	5/10	0/10
t-C ₄ H ₉	10	120	2/10	0/10
	30	120	2/10	0/10
	100	120	5/10	0/10
C ₂ H ₅	3	120	1/5	0/5
	10	120	1/5	0/5
	30	120	2/5	0/5
	100	120	5/5	0/5
(CH ₃) ₂	30	120	4/5	0/5
	100	120	4/5	0/5
n-C ₄ H ₉	10	120	1/10	0/10
	30	120	3/10	0/10
	100	120	4/10	0/10
s-C ₄ H ₉	3	120	2/10	0/10
	10	120	3/10	0/10
	30	120	2/10	0/10
i-C ₄ H ₉	0.3	120	1/10	0/10
	0.8	120	3/10	0/10
	2.0	120	5/10	0/10
	5.5	120	7/10	0/10
	14.4	120	9/10	0/10
n-C ₃ H ₇	3	120	2/10	0/10
	10	120	2/10	3/10
	100	120	3/10	0/10

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i-C ₃ H ₇	10	120	5/10	1/10
	30	120	5/10	0/10
	100	120	6/10	0/10
C ₆ H ₅	100	120	0/10	0/10
neo-C ₅ H ₁₁	10	120	2/10	0/10
	30	120	4/10	0/10
	100	120	4/10	0/10

- High-intensity corneal electroshock consisted of 50 mA, base-to-peak sinusoidal current for 0.2 sec. All other data was from low-intensity electroshock, 17 mA base-to-peak sinusoidal current for 0.2 sec.

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TABLE 3

Threshold Maximal Electroshock with Isobutyl GABA.

<u>Time of Testing</u>	<u># Protected</u>
1 hr.	2/10
2 hr.	8/10
4 hr.	4/10
8 hr.	2/10

TABLE 4

<u>Dose m/k</u>	<u># Protected</u>
0.3	1/10
0.8	3/10
2.0	5/10
5.5	7/10
14.4	9/10

TABLE 5

Maximal electroshock data:

R	dose (mg/kg)	time after effect dose (min)	# protected/ # tested	ataxia # ataxic/ # tested
i-C ₄ H ₉	10	120	1/5	0/5
i-C ₄ H ₉	30	120	4/5	0/5
i-C ₄ H ₉	100	120	4/5	0/5

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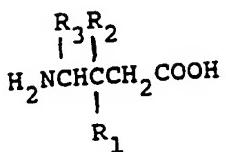
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what is claimed is:

1. A compound of the formula

5



wherein R_1 is a straight or branched alkyl of from
 10 one to six carbons, a phenyl, or a cycloalkyl having
 from 3 to 6 carbon atoms, R_2 is hydrogen or methyl,
 and R_3 is hydrogen; methyl or carboxyl; or its
 diastereomers; or enantiomers; and both
 pharmaceutically acceptable salts thereof.

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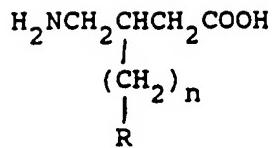
2. A compound as set forth in claim 1
 wherein R_3 is hydrogen, R_2 is hydrogen, and R_1 is
 $-(\text{CH}_2)_n-\text{iC}_4\text{H}_9$ as an (R), (S) or (R,S) isomer, n
 being 0-2.

20

3. A compound as set forth in claim 2 and
 being 4-amino-3-(2-methylpropyl)butanoic acid.

4. The use of a compound for treating
 25 seizure disorders in a patient which comprises
 administering to the patient an effective amount of
 the compound of the formula

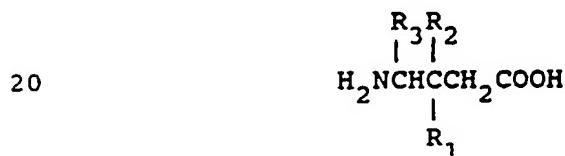
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5 wherein R is an isobutyl; n is zero, one, or two and
its enantiomers or a pharmaceutically acceptable salt
thereof.

5. The use of a compound as set forth in
10 claim 4 wherein the compound is 4-amino-3-(2-
methylpropyl)butanoic acid or a pharmaceutically
acceptable salt thereof.

6. A method of treating seizure disorders
15 in a patient, said method including the steps of
administering an anticonvulsant effective amount of a
composition having the formula



wherein R₁ is a straight or branched alkyl of from
one to six carbons, a phenyl or a cycloalkyl of 3 to
25 6 carbons, R₂ is hydrogen or methyl, and R₃ is
hydrogen, methyl or carboxyl; or its diastereomers;
or enantiomers; and pharmaceutically acceptable salts
thereof.

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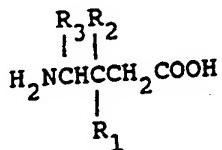
-24-

7. A method as set forth in claim 6
 wherein the compound is 4-amino-3-(2-methylpropyl)butanoic acid.

5 8. A method as set forth in claim 6
 wherein said administering step is further defined as
 orally administering the compound.

9. A method as set forth in claim 4
 10 wherein said administering step is further defined as
 intravenously administering the compound.

10. A pharmaceutical composition for
 treating seizures comprising an anticonvulsant
 15 effective amount of a compound of the formula



20 wherein R_1 is a straight chain or branched alkyl of
 from one to six carbons, a phenyl or a cycloalkyl of
 three to six carbons, R_2 is hydrogen or methyl, and
 R_3 is hydrogen, methyl or carboxyl; or its
 25 diastereomers; or enantiomers; and pharmaceutically
 acceptable salts thereof and pharmaceutical carrier.

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11. A pharmaceutical as set forth in claim
10 wherein R₃ is hydrogen, R₂ is hydrogen, and R₁ is
-(CH₂)_n-i C₄H₉ as an (R), (S) or (R,S) isomer, n
being 0-2.

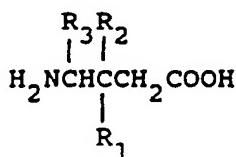
5

12. A pharmaceutical as set forth in claim
11 wherein the active ingredient is 4-amino-3-(2-
methylpropyl)butanoic acid.

10 13. A method of increasing brain neuronal
GABA levels, said method including the steps of:
systemically administering an effective amount of a
3-alkyl-4-aminobutyric acid or a 3-alkylglutamic acid
and activating brain neuronal L-glutamic acid
15 decarboxylase activity.

14. A method as set forth in claim 13
wherein said administering step is further defined as
administering a compound of the formula

20



25 wherein R₁ is a straight chain or branched alkyl of 1
to 6 carbons, a phenyl or a cycloalkyl of 3 to 6
carbon atoms, R₂ is -H, -CH₃ or -CH₂ and R₃ is -H or

-COOH, its diastereomers and enantiomers, and both pharmaceutically acceptable base salts and acid addition salts thereof.

5 15. A method as set forth in claim 14
wherein the compound is 4-amino-3-(2-methylpropyl)butanoic acid.

10 16. A method as set forth in claim 14
wherein the compound is 4-amino-3-(2-methylpropyl)glutamic acid.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/08701

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): C07C 229/08, 24, 28, 34, 36; A61K 31/195

U.S. CL: 514/561,567; 562/443,504,505,506,507,553,571

II. FIELDS SEARCHED

Minimum Documentation Searched ?

Classification System	Classification Symbols
U.S.	514/561,567; 562/443,504,505,506,507,553,571

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages ***	Relevant to Claim No. ***
A	US, A, 2,628,980 (MOE) 17 FEBRUARY 1953 See Column 4..	1-3, 10-12
X A	JP, B, 49-40460 (DAIICHI SEIYAKU CO. LTD) 02 NOVEMBER 1974. See Abstract.	1-3, 10-12 4-9, 13-16
X A	Journal of Medicinal Chemistry, Volume 8, issued 1965 (EASTON, PENNSYLVANIA) Y.C. KIM, "Glutamic Acid Analogs," see pages 509-513.	1,10 2-9,11-16

* Special categories of cited documents: **

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family.

IV. CERTIFICATION

Date of the Actual Completion of the International Search

27 FEBRUARY 1992

Date of Mailing of this International Search Report

12 MAR 1992

International Searching Authority

ISA/US

Signature of Authorized Officer

Jerome L. Shippen
MICHAEL L. SHIPPEN

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